General

Guideline Title

Appropriate surgical margins and proper handling of soft tissue sarcoma of the extremities.

Bibliographic Source(s)

Kandel R, Coakley N, Werier J, Engel J, Verma S, Sarcoma DSG. Appropriate surgical margins and proper handling of soft tissue sarcoma of the extremities. Toronto (ON): Cancer Care Ontario (CCO); 2012 Sep 7. 39 p. (Evidence-based series; no. 11-10). [70 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

- In limb salvage surgery for soft tissue sarcoma (STS), surgery should be planned with the objective of achieving a clear margin. However, in order to preserve functionality, surgery may result in a close or even microscopically positive margin. Based on the consensus opinion of the Sarcoma Disease Site Group (DSG), a 'close' margin is considered to be <1 cm following formalin fixation. In the circumstance of a close or microscopically positive margin, the use of preoperative or postoperative radiation may be considered.
- For the histological assessment of margins, no definitive recommendations can be made for the appropriate number of margin samples that are required.
- It is not possible to make evidence-based recommendations as to the appropriate handling of surgical resection specimens to assess the adequacy of excision. Guidelines, where mentioned, endorse inking margins and sampling them perpendicular to (and not enface to) the margin.
- In the absence of evidence-based recommendations, the Sarcoma DSG recommends the following, based on the expert opinion of the Working Group and consensus of the DSG members:
    - The specimen should be received fresh with orientation indicated by the surgeon.
    - The specimen and the tumour should be measured in three dimensions.
    - The distances from all six margins should be measured and the location of the tumour (superficial or deep) and the relationship to fascia, if present, indicated.
    - All margins should be sampled perpendicular to the margin, and at least 2 samples taken from the closest margin and 1 to 2 sections

from all other margins.
- More extensive margin sampling should be considered for tumours such as angiosarcoma, epithelioid sarcoma, and chondrosarcoma.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Soft tissue sarcoma (STS) of the extremities

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Oncology

Pathology

Radiation Oncology

Surgery

Intended Users

Physicians

Guideline Objective(s)

- To evaluate, in limb salvage surgery for extremity soft tissue sarcoma (STS), what is considered an adequate surgical margin, in the context of the following:
  - Surgery alone
  - Surgery in combination with adjuvant or neoadjuvant radiation and/or chemotherapy
- To evaluate the appropriate number of surgical resection specimens
- To evaluate the appropriate handling technique for surgical resection specimens

Target Population

Patients with soft tissue sarcoma (STS) of the extremities who are candidates for limb-sparing surgery and whose treatment objectives are to obtain local control and overall survival

Interventions and Practices Considered

1. Limb salvage surgery

2. Preoperative or postoperative radiation
3. Appropriate handling of surgical resection specimens
    - Inking margins
    - Sampling perpendicular to margin

Major Outcomes Considered

- Recurrence free survival
- Overall survival

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

The MEDLINE (1975 to June 2011), EMBASE (1975 to June 2011), and Cochrane Library (2011, Issue 2) databases were searched for published practice guidelines, technology assessments, systematic reviews, clinical trials, and studies. Reference lists of papers and review articles were scanned for additional citations.

- The Canadian Medical Association InfoBase (https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx)
- National Guideline Clearinghouse (http://www.guideline.gov/)
- And other websites were searched for existing evidence-based practice guidelines.

The American Society of Clinical Oncology (ASCO) Conference proceedings from 2007 to 2010 were searched. Search terms indicative of sarcoma, surgical margins, and handling of specimens were used, with the full search strategy available in Appendix B in the original guideline document.

Study Selection Criteria

Inclusion Criteria

Articles were eligible for inclusion in this systematic review of the evidence if they reported on studies that met the following criteria:

- The definition of what was considered to be a negative or positive margin through measurements or detailed descriptions was reported.
- They included adult patients with extremity (arms and legs) soft tissue sarcoma (STS) and limb-sparing surgery was the primary treatment.
- They reported on at least one of the following outcomes: local recurrence, recurrence free survival, overall survival, or disease free survival.
- For Questions 2 and 3 (in the original guideline document), they reported on an outcome resulting from the handling techniques for STS specimens.

Exclusion Criteria

Studies were excluded if they:

- Were published in a language other than English as translation capabilities were not available.
- Included patients with other types of sarcoma and the results for STS were not specifically reported.
- Did not specify what constituted a negative or positive surgical margin.

- Were retrospective studies with less than 100 subjects.

Number of Source Documents

Thirty-three papers, including four guidelines, one protocol, and one abstract, were eligible for inclusion in this systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Quality Appraisal of Evidence

The Appraisal of Guidelines Research and Evaluation (AGREE) tool was used by four independent methodologists to evaluate the quality of the identified evidence-based guidelines. While all the scoring domains of the AGREE tool were considered in the evaluation of guidelines, the Rigour of Development domain, describing the rigour of systematic methods in identifying and evaluating evidence, along with the Overall Rating, were considered to be most relevant in application for this systematic review. The AGREE Tool scoring results can be found in Appendix C of the original guideline document.

Synthesizing the Evidence

Data was not pooled in a meta-analysis due to the absence of randomized trial (RCT) data and the heterogeneity of the included studies. Very few eligible studies reported hazard ratios (HR) of primary outcomes such as overall survival, and in many studies the appropriate data were not available to estimate HR.

Statistical heterogeneity would be calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Development and Internal Review

This Evidence-Based Series (EBS) report was developed by the Sarcoma Disease Site Group (DSG) of the Cancer Care Ontario Program in Evidence-based Care (CCO PEBC). The Sarcoma DSG consists of surgeons, pathologists, and medical and radiation oncologists (see Section 2: Appendix A in the original guideline document). Where evidence was not available or was not sufficient to reach a conclusion for the recommendations the Working Group made recommendations based on expert opinion.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel (RAP) Review and Approval

Prior to the submission of this Evidence-Based Series (EBS) draft report for External Review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) RAP, a panel that includes oncologists and whose members have clinical and methodological expertise.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Guideline Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC RAP, the guideline authors circulated Sections 1 and 2 to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, four targeted peer reviewers from Canada considered clinical and/or methodological experts on the topic were identified by the guideline authors. Several weeks prior to the completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on June 12, 2012. Follow-up reminders were sent at two weeks and at four weeks. All the targeted peer reviewers were required to complete the conflict of interest form. Two reviewers (WT and TN) finished their questionnaires and one reviewer (JW) joined *Professional Consultation* below.

Professional Consultation

Sixty potential participants were identified by the guideline authors. Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base (Section 2 in the original guideline document). The notification email was sent on June 11, 2012. Two follow-up reminders were sent on June 25 and July 9, 2012.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Sarcoma Disease Site Group (DSG), the Gynecology Cancer DSG, and the Working Group.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by prospective studies, retrospective studies, and guidelines.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Twenty-eight studies provided evidence on margin status and recurrence rates. Local recurrence rates ranged from 3% to 24% for patients with negative margins and from 6% to 53% for positive margins.
- Two studies provided recurrence free survival rates for extremity soft tissue sarcoma (STS) treated with surgery alone. They both concluded that positive margin status was associated with increased recurrence rate.
- Twenty-four studies evaluated the use of radiotherapy (RT) in addition to the resection of STS. Of those studies, three provided separate results for RT versus no radiotherapy. Two of these studies demonstrated no difference in local recurrence rates between the groups, and the third showed that RT decreased the frequency of local recurrence.
- Only one study provided results for the use of chemotherapy in addition to surgery and radiation in patients with marginal excisions (incisions through the pseudocapsule or reactive zone). No significant benefit was observed.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- In limb-sparing surgery for soft tissue sarcoma (STS), an adequate margin for surgical treatment alone or for surgery with radiotherapy (RT) cannot be defined as the studies did not definitively identify an appropriate margin distance. Intact fascia (which can be measured in millimeters) is considered an adequate margin by some.
- A microscopic positive margin in STS of the limb treated with surgery and radiation may have an increased rate of local recurrence. This suggests that every effort should be made to achieve a negative margin.
- In the event that limb function will be compromised, surgeons and patients may wish to discuss the benefits and risks of maintaining a microscopically positive margin and the role of postoperative RT.
- Local recurrences have been observed even when negative margins are achieved with surgery and with surgery and radiation, suggesting that tumour characteristics other than margin status are important. Further study is required.
- At this time, there is no evidence to support the use of postoperative chemotherapy in soft tissue tumours of the extremity that have undergone intralesional or marginal excisions.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Kandel R, Coakley N, Werier J, Engel J, Verma S, Sarcoma DSG. Appropriate surgical margins and proper handling of soft tissue sarcoma of the extremities. Toronto (ON): Cancer Care Ontario (CCO); 2012 Sep 7. 39 p. (Evidence-based series; no. 11-10). [70 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Sept 7

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario Initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Guideline Committee

Sarcoma Disease Site Group (DSG)

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest Policy, the guideline authors, the Sarcoma Disease Site Group (DSG) members, and internal and external reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site .

Availability of Companion Documents

The following are available:

- Appropriate surgical margins and proper handling of soft tissue sarcoma of the extremities. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2012 Sep 7. 6 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site .
- Program in Evidence-based Care (PEBC) handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012, 14 p. Electronic copies: Available in PDF from the CCO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on September 5, 2013.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.